Utility of Complementary Molecular Reactivity and Molecular Recognition (CMR/R) Technology and Polymer-Supported Reagents in the Solution-Phase Synthesis of Heterocyclic Carboxamides

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The use of our recently reported chemical library purification strategy in the development of a herbicidal lead, *N*-(3-benzoylphenyl)-3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazole-5-carboxamide (**3**), is described. The approach applying fundamental properties of complementary molecular reactivity and molecular recognition (CMR/R) as the basis for a general purification strategy was utilized. Polymeric reagents were used in the synthesis to generate reactive species involved in product formation, and complementary molecular reactivity/molecular recognition polymer **8** (CMR/R polymer **8**) was used in the solution-phase syntheses of building blocks, primary libraries, and lead refinement libraries. An extension of the CMR/R methodology was applied, utilizing a sequestration enabling reagent (SER), transforming a reactant into an electrophilic species sequestrable by CMR/R polymer **8**. This library purification strategy enabled rapid lead generation and lead refinement to afford herbicide **27o**. The CMR/R solid-phase purification technique enabled a simple, general, and powerful protocol, eliminating the usual tedious and time-consuming methods required for solution-phase product purification. The result was the synthesis of hundreds of compounds, prepared in a relatively short time, leading to a compound with a 4-fold improvement in herbicidal activity over the initial lead.

Introduction

Combinatorial chemistry has become a powerful tool for drug discovery in the pharmaceutical arena[1] and has recently found utilization in other areas.[2] As a result, combinatorial synthesis of libraries containing small organic molecules has become a rapidly evolving area of research. While both solid-phase[3] and solution-phase[4] synthetic techniques have been employed to generate libraries, the majority of the compound libraries have been synthesized on a solid support. The solid support technique offers many advantages: two of the more important advantages being the ease of separating the product away from the reaction medium and the manipulation of the beads using volumetric techniques. Limitations of the solid support technique have included reaction-scale restriction (amount of the solid support and its loading capacity) and the need for validation of heterogeneous reactions. Solution-phase synthetic techniques have the advantage of nonlimiting scale and can be easily manipulated as well. Moreover, organic reactions performed in solution phase decrease the validation time. However, in a solution-phase synthesis, isolation or purification of the reaction products away from the reaction medium, e.g., reactants, reagents, side products, etc., may prove to be a difficult task, especially for mixtures of products. A recently described strategy based on principles of complementary molecular reactivity and

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Scheme 1

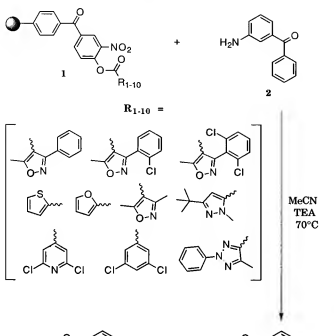
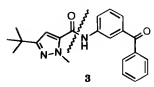
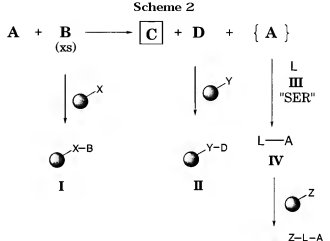


Chart 1



Scheme 2



recognition (CMR*R*) employs both solid-phase techniques with solution-phase synthesis.[5,6] The CMR*R* strategy relies on inherent or artificially imparted molecular recognition and/or molecular reactivity functionality as the basis for product purification and isolation. We would like to report the successful use of this CMR*R* strategy for the development of a herbicidal lead to generate heterocyclic carboxamides as potential herbicides. Polymeric reagents were used in the synthesis to generate reactive species for product formation, and solution-phase CMR*R* scavenging resins were used to remove unreacted or derivatized starting materials from solution-phase product mixtures affording purified product by direct filtration. This technique was utilized in the preparation of building blocks (BB), primary screening libraries, and lead refinement libraries. This simple and general strategy enabled all syntheses to be performed in a high-speed parallel fashion.

Results and Discussion

In a recent communication,[7] a library of 8000 compounds containing amides and esters was prepared by reacting a single nucleophile with a mixture of polymer-bound activated esters. One such mixture was prepared as shown in Scheme 1. Polymer **1** containing a mixture of activated heterocyclic esters was reacted with 3-aminobenzophenone (**2**) to afford a mixture of 10 amides. This mixture exhibited herbicidal activity in a high-throughput whole plant assay, and *N*-(3-benzoylphenyl)-3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazole-5-carboxamide (**3**) was found to be responsible for the herbicidal activity. It controlled (80% or better) several weed species at 100 g/ha and exhibited symptoms as low as 10 g/ha.

In an effort to increase the herbicidal activity, synthetic efforts to prepare analogs based on lead compound **3** were initiated. Pure compounds in known quantities would be required to develop the structure-activity relationship (SAR), and it was desirable for the synthesis to be amenable to a high-speed parallel methodology. The pyrazolecarboxamide **3** itself offers many possibilities for analog synthesis and initial SAR work. We approached analog synthesis by considering the molecule as being composed of two halves (Chart 1). Syntheses allowing for variations on both sides of the molecule were then developed. The first approach involved variation of the pyrazole, including alternative heterocycles, while leaving the aniline side constant, and the second approach involved synthesis directed at variations of the aniline side leaving the pyrazole portion constant.

The CMR*R* methodology was used for the synthesis of analogs of the lead compound **3** enabling a high-speed parallel format. Scheme 2 illustrates the CMR*R* approach for a chemical library step which relies on the inherent molecular reactivity properties of reactants[8] and/or the inherent molecular recognition properties of byproducts as the basis for product purification and isolation. In parallel reaction vials, excess reactants **B** are utilized to drive the solution-phase reactions of **A** to completion (formation of products **C**). After the reactions are complete, the excess reactants **B** are selectively removed from each reaction medium by CMR*R* resin **X**

(5) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. S. *J. Am. Chem. Soc.* **1997**, *119*, 4874–4881.

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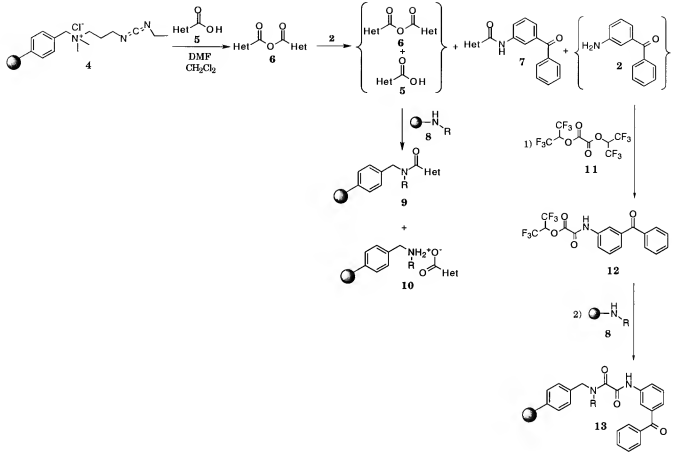
(8) The terms reactant and reagent have explicit meanings in the context of this strategy. A reactant is a starting material which becomes chemically incorporated into the product. A reagent is a chemical which mediates a transformation but does not become incorporated into the product.

Scheme 3

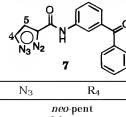


Resin **X** contains functionality complementary to the reactive functionality of **B**. Reaction with, and sequestration of, the remaining excess **B** forms the polymer-bound adducts **I**. Simple incubation of the parallel reaction mixtures with resin **X**, followed by filtration and concentration, affords purified product **C**. If sequestrable byproducts **D** (containing inherently accessible molecular recognition functionality) are also formed, the concomitant use of a second CMR/R resin (**Y**) is also used to chemoselectively sequester **D** as the polymer-bound adducts **II** (resin **I** could contain molecular recognition functionality complementary to **D**, thus utilizing only one resin). If the reaction can not be driven to completion and the reaction medium has remaining reactant **A**, a sequestration enabling reagent (SER) (**III**) is added, transforming **A** into a species (**IV**) sequestrable by CMR/R resin **Z** as the polymer-bound adducts **V**.

It was envisioned that a CMR/R approach for preparation of heterocyclic carboxamides could be accomplished through a simple amide bond-forming reaction. Thus, reacting heterocyclic acid chlorides with 3-aminobenzophenone (**2**) would afford analogs with variations of the pyrazole and alternative heterocycles. However, few heterocyclic carboxylates are available as acid chlorides. Converting the more readily available heterocyclic carboxylic acid to the acid chloride would require an additional step, and a single condition for acid chloride formation would be unlikely to be compatible for all heterocycles used. Taking advantage of the dehydrating power of polymer-bound 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (P-EDC)[9] (**4**), it was found that heterocyclic carboxylic acids could be easily converted into their respective anhydrides (**6** in Scheme 3). The anhydride in turn could then be reacted with the aniline **2** to afford the carboxamide product. In this procedure, determining the appropriate amount of P-EDC (**4**) to be used for the reaction was critical. The diimide loading of polymer **4** was determined by mixing a weighed amount of P-EDC (**4**) in deuteriochloroform at 0°C with an excess of acetic acid (carefully measured). The solution was stirred for 15 min at room temperature, filtered, and analyzed by ^{1}H NMR. The integration ratio of acetic acid to acetic anhydride was determined, and the amount of anhydride formed was calculated. Using this technique, it was possible to calculate the precise loading of available carbodiimide in **4**. For a single batch of **4**, the loading was determined to be 0.917 mmol/g (based on the loading of the Merrifield's resin used to make the P-EDC and assuming 100% conversion of Merrifield's resin to P-EDC, the theoretical loading of carbodiimide was calculated to be 0.914 mmol/g). Scheme 3 shows the optimized synthesis in which 1.5 equiv of P-EDC (**4**) was stirred with 3.0 equiv of the heterocyclic carboxylic acid **5** in dichloromethane at 0°C for 15 min, at which point the anhydride **6** was formed. The solution was stirred at room temperature for 30 min, and 1.0 equiv of the aniline **2** was added, and the slurry was heated to 50°C. In some cases, the reactions were slow enough to require up to 7 days for completion. After total consumption of the aniline **2** was observed by GC, the reaction contained the product **7**, excess anhydride **6**, byproduct acid **5**, and reacted P-EDC. The CMR/R amine polymer **8** was added

(9) Desai, M. C.; Stramiello, S. L. M. *Tetrahedron Lett.* **1993**, *34*, 7685.

Table 1. Carboxamides 7a–r Containing a Pyrazole Heterocycle Prepared by the Synthesis in Scheme 3



7

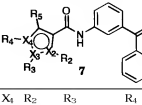
compd	N_2	N_3	R_4	R_5	% yield[b]
7a	Me		*neo*-pent	H	86
7b	Me		Me	H	93
7c[a]	Me		Me	Br	93
7d[a]	Me		H	H	77
7e	Me		CF_3	H	99
7f[a]	Me		CF_3	Cl	88
7g[a]	Me		4-Cl-2-F-benzene	Cl	67
7h[a]	Et		H	H	63
7i	$PhCH_2$		*t*-Bu	H	91
7j	*t*-Bu		Me	H	69
7k		Me	*t*-Bu	H	48
7l		Me	*neo*-pent	H	100
7m		Me	Me	H	93
7n[a]		Me	Cl	Cl	82
7o[a]		Me	CO_2Me	H	82
7p[a]		Me	CF_3	H	81
7q[a]		Me	CF_3	Br	66
7r[a]		Ph	Me	H	77

[a] Addition of **11** was required for removal of aniline. [b] Yields are based on mass recovery.

and reacted with anhydride **6** and also sequestered the heterocyclic acid byproduct **5**, forming polymer-bound adducts **9** and **10**. Simple filtration and rinsing with dichloromethane yielded a filtrate whereupon evaporation of the solvents left highly purified product **7**.

In the synthesis shown in Scheme 3, some of the reactions could not be driven to completion even with a large excess of anhydride and/or extended reaction times. In these cases, the product mixtures contained product **7**, anhydride **6**, heterocyclic carboxylic acid **5**, and also unreacted aniline **2**. CMR/R polymer **8** could not remove the aniline **2** from the mixture in its present form. Thus, it was anticipated that a SER could be added that would react with the aniline **2**, transforming it into an electrophilic species sequestrable by CMR/R polymer **8**. This strategy was realized by reacting hexafluoroisopropyl oxalate (**11**) with aniline **2** resulting in exclusive formation of the monoaddition product **12** (shown in Scheme 3) possessing an activated ester to react with the CMR/R amine polymer **8**. After the mixture stirred at 50 °C for 1 h, the CMR/R polymer **8** was added to remove the anhydride **6**, the heterocyclic carboxylic acid **5**, and any remaining SER **11**, as well as the derivatized aniline **12**, leaving pure product **7** after simple filtration.[10] This procedure clearly demonstrates how a purification strategy based on principles of complementary molecular reactivity and molecular recognition (CMR/R) can be employed in a solution-phase synthesis to purify a reaction mixture that would otherwise require a tedious, time-consuming purification process. Moreover, strategies for sequestration of multiple solution-phase species (**5**, **6**, **11**, and **12**) with a single CMR/R resin further illustrate the power of this method. Compounds prepared by this route are shown in Tables 1–3.[11]

Table 2. Carboxamides 7A–Z Containing a 5-Membered Heterocyclic Ring Prepared by the Synthesis in Scheme 3

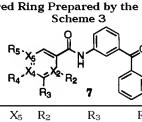


7

compd	X_2	X_3	X_4	R_2	R_3	R_4	R_5	% yield[b]
7A[a]	S	C	C		H	H	H	100
7B	S	C	C		*t*-Bu	H	H	93
7C[a]	S	C	C		Cl	H	H	87
7D[a]	S	C	C		H	3-thiophene	H	60
7E[a]	O	C	C		H	H	H	100
7F[a]	O	C	C		H	*t*-Bu	H	75
7G[a]	O	C	C		*t*-Bu	H	H	83
7H[a]	O	C	C		$SiMe_3$	H	H	80
7I[a]	O	C	C		Cl	Cl	H	84
7J	O	C	C		Me	Me	H	93
7K[a]	C	O	C	Me		Me	H	53
7L[a]	C	O	C	Me		Ph	H	78
7M	S	C	N		Me		Me	100
7N[a]	S	C	N		*i*-Pr		Me	83
7O[a]	S	C	N		OMe		CF_3	75
7P[a]	S	C	N		Cl		*i*-Pr	79
7Q[a]	S	C	N		H		Me	94
7R[a]	S	C	N		H		Br	36
7S	S	C	N		4-Cl-Ph		Me	70
7T	S	C	N		Ph		Me	77
7U	S	C	N		4-CF_3-Ph		Me	65
7V	S	C	N		3-CF_3-Ph		Me	64
7W[b]	S	C	N		Cl		Ph	72
7X[a]	O	C	N		NH*t*-Bu		CF_3	70
7Y[a]	S	N	C			Cl	Cl	35
7Z[a]	N	N	N			3-CF_3-Ph	Me	67

[a] Addition of **11** was required for removal of aniline. [b] Yields are based on mass recovery.

Table 3. Carboxamides 7aa–ll Containing a 6-Membered Ring Prepared by the Synthesis in Scheme 3



7

compd	X_2	X_4	X_5	R_2	R_3	R_4	R_5	% yield[b]
7aa	C	C	C	CF_3	H	H	H	49
7bb	C	C	C	H	CF_3	H	H	81
7cc	C	C	C	H	H	CF_3	H	100
7dd	C	C	C	H	H	Cl	H	93
7ee	C	C	C	F	H	F	H	96
7ff	C	C	C	NO_2	H	CF_3	H	97
7gg[a]	C	C	C	*t*-Bu	H	*t*-Bu	H	73
7hh	C	C	C	H	CHMe(CN)	H	H	86
7ii	N	C	N		H	H	H	100
7jj	N	C	N		H	Me	H	95
7kk[a]	N	C	C		Cl	H	CF_3	71
7ll	C	N	C	H	Cl		Cl	83

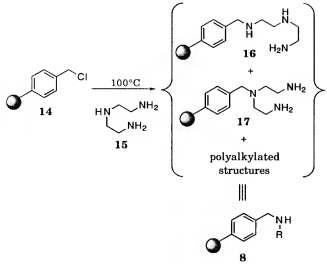
[a] Addition of **11** was required for removal of aniline. [b] Yields are based on mass recovery.

The CMR/R polyamine polymer **8** was prepared as shown in Scheme 4 by taking Merrifield's resin (**14**) (2% cross-linked) and heating to 100 °C in diethylenetriamine (**15**) for 4 h followed by rinsing with base to remove residual salts. Diethylenetriamine (**15**) was used as the solvent to minimize the amount of cross-linking. Compound **15** can displace the chlorine by attack of the primary nitrogen or the secondary nitrogen to afford either secondary or tertiary amines (**16** or **17**). Because of the complex nature of the polymer, containing primary,

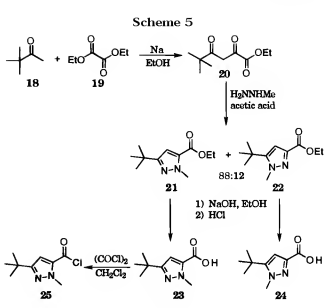
(10) Further experiments demonstrated that succinic anhydride and tetrafluorophthalic anhydride also worked to derivatize the aniline for removal.

(11) All of the compounds depicted in Tables 1–7 were characterized by GC/MS and reported with yields, with a random 60% of the compounds characterized by ^1H NMR.

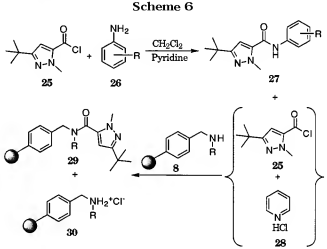
Scheme 4



Scheme 5



Scheme 6



secondary, and tertiary amines, the resin will be drawn herein as the generic form **8**. Combustion analysis showed that all of the chloride atoms were completely displaced and that the CMR/*R* polymer **8** contained 2.36 mmol/g nitrogen. This analysis would fit a polymer with 64% monoalkylation and 36% dialkylation (cross-linking). Commercial polymer-bound amines could have been utilized; however, the use of a triamine such as **15** yielded a polyamine polymer with a much higher scavenging capacity and was much more economical. Typically the polymer **8** has 2–3 times the loading capacity than that of the commercially available polyamine polymers at a 4–10 times lower cost.

After biological evaluation of the analogs from Tables 1–3, it was determined that the original pyrazole (Chart 1) was optimal for activity. Thus, our attention turned to variation of the aniline side leaving the pyrazole portion constant. Since rapid preparation of analogs, in which the aniline portion was varied, could be done by reacting the pyrazole acid chloride with various anilines, it was necessary to prepare the pyrazole acid chloride on larger than normal scale, as shown in Scheme 5.[12]

Using the CMR/*R* strategy, the pyrazole acid chloride **25** was coupled with anilines **26** to prepare analogs in a high-speed fashion as single compounds per well (Scheme 6). Compound **25**, 1.2 equiv, was reacted with the aniline **26** in dichloromethane in the presence of pyridine. The excess **25** assures total consumption of the aniline **26**, leaving product **27**, acid chloride **25**, and pyridine hydrochloride (**28**) as the product mixture. The CMR/*R* strategy was utilized in the purification of the product mixture. The polyamine CMR/*R* polymer **8** (scavenger) was added to each product mixture vessel. The CMR/*R* polymer **8** sequestered the remaining acid chloride **25** and also removed the hydrochloric acid salt (byproduct) from the pyridine leaving a solution of pyridine and product **27** in dichloromethane. Simple filtration and rinsing with dichloromethane yielded a filtrate whereupon evaporation of the solvents left highly purified product **27** from each parallel reaction. This illustrates a simple, general, and powerful purification protocol allowing the synthesis to be performed in a high-speed parallel fashion.

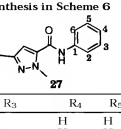
Compounds **27** prepared by the synthesis described in Scheme 6 are shown in Table 4. The anilines **26** used were commercially available or retrieved from our in-house compound archive. Compounds **27a**–**cc** had a multitude of substituents on the phenyl ring with a large number containing a carbonyl functionality at the 3-position. Compounds **27dd**–**hh** were directed at analogs of the lead **3** with various linking groups between the two phenyl rings at the 3-position. Compounds **27ii**,**jj** are both regioisomers of the lead **3**.

Figure 1 shows the GC/MS profile of three compounds prepared by the solution-phase CMR/*R* strategy of Scheme 6. Included is a GC/MS profile of **27s** taken before the addition of the CMR/*R* polymer **8**, and the second is after purification utilizing polymer **8**. The latter GC/MS tracing, with complete sequestrative removal of excess acid chloride **11**, indicates highly purified product **27s**.

(12) The pyrazole acid chloride **25** was synthesized in the straightforward fashion shown in Scheme 5. Pinacolone (**18**) was added dropwise to a solution of ethyl oxalate (**19**) and sodium ethoxide to afford the ethyl ester of 5,5-dimethyl-2,4-dioxohexanoic acid (**20**). Compound **20** was condensed with methylhydrazine to afford an 88:12 ratio of regioisomers 3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazole-5-carboxylic acid, ethyl ester (**21**) and 5-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid, ethyl ester (**22**), respectively, which were separated using silica gel. Compounds **21** and **22** were each separately hydrolyzed to 3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazole-5-carboxylic acid (**23**) and 5-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (**24**), respectively. The free acid **23** was converted to 3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazole-5-carbonyl chloride (**25**) using oxalyl chloride. Structural assignments of regioisomers **23** and **24** are based on ^{13}C NMR chemical shifts and comparisons with regiochemically known hydoxypyrazoles.[13]

(13) Hamper, B. C.; Kurtzweil, M. L.; Beck, J. P. *J. Org. Chem.* **1992**, *57*, 5093.

Table 4. Pyrazolecarboxamides 27 Prepared by the Synthesis in Scheme 6



27

compd	R_2	R_3	R_4	R_5	R_6	% yield[b]
27a	H	H	H	H	H	100
27b	H	COMe	H	H	H	100
27c	H	COMe	NO_2	H	H	62
27d	H	COMe	Me	H	Me	100
27e	H	COMe	H	H	Cl	88
27f	H	COPr	H	H	H	92
27g	H	$COCH_2CH_2$		H	H	82
27h	H	$CO(CH_2)_4$		H	H	88
27i	H	$COCO_2$		H	H	96
27j	H	CONMeCO		H	H	75
27k	H	COCONH		H	H	79
27l	H	CO_2Me	H	H	H	43
27m	H	CO_2Et	H	H	H	100
27n	H	$CONH_2$	H	H	H	100
27o	H	$CONEt_2$	H	H	H	98
27p	H	$COCH_2CONH$-2-isothiazole	H	H	H	70
27q	H	$COCH_2CO_2Et$	H	H	H	93
27r	H	$NHCO_2t$-Bu	H	H	H	81
27s	H	OMe	OMe	H	H	94
27t	H	OMe	H	H	H	82
27u	H	$OCH(Me)_2$	H	H	H	100
27v	H	CF_3	H	H	H	100
27w	H	NO_2	H	H	H	99
27x	$SiMe_3$	H	H	H	H	96
27y[a]	CF_3	H	NO_2	H	H	68
27z	Cl	H	Cl	H	H	96
27aa[a]	Cl	H	SO_2Me	H	H	86
27bb	Cl	H	F	OMe	H	100
27cc	F	H	F	H	H	80
27dd	H	Ph	H	H	H	87
27ee	H	SO_2Ph	H	H	H	75
27ff	H	OPh	H	H	H	100
27gg	H	NHCOPh	H	H	H	81
27hh	H	CONHPh	H	H	H	69
27ii	COPh	H	H	H	H	82
27jj	H	H	COPh	H	H	84

[a] Prepared by reacting **25** with the aniline **26** in pyridine at 80°C. [b] Yields are based on mass recovery.

These GC/MS chromatograms are representative and demonstrate the purity obtained using the CMR/R polymer **8**.

A series of 3-aminobenzophenone building blocks were required to prepare analogs of similar structure to the lead compound **3**. The CMR/R polymer **8** played a major role in the preparation of new 3-aminobenzophenone building blocks, permitting their synthesis in a high-speed, solution-phase, parallel format. Two solution-phase strategies were devised to prepare 3-aminobenzophenones. The first strategy is shown in Scheme 7A. Friedel–Crafts acylation using 1.3 equiv of 3-nitrobenzoyl chloride (**31**), with 1 equiv of an electron-rich substituted benzene (**32**) was carried out in 1,2 dichloroethane with aluminum trichloride. An excess of **31** was used to assure total consumption of the substituted benzene **32**. Upon completion, an aqueous extraction was utilized to remove the salts, leaving 3-nitrobenzophenone **33**, excess acid chloride **31**, and trace amounts of water. Purification at this point was accomplished by addition of magnesium sulfate and the CMR/R polymer **8** together, followed by stirring the slurry for 15 min. After the polymer was filtered and rinsed, the solvent was removed to afford the pure substituted 3-nitrobenzophenones **33**. In the cases where benzene **32** contained an alkoxy substituent, the Friedel–Crafts acylation reaction mixture was stirred at room temperature for 4 h to avoid dealkylation. Because of the large variety of substituents in the nitrobenzophenones **33**, a relatively selective reducing agent was required. It was found that reduction using iron gave excellent results and could be used in a parallel fashion. The 3-nitrobenzophenones **33** were reduced with powdered iron in acetic acid at 80 °C to afford 3-aminobenzophenone **34** building blocks substituted with electron-donating substituents on the phenyl ring. In some cases, the substituted 3-aminobenzophenones **34** required purification which was accomplished using preparative thin layer chromatography.

The second synthesis for preparing the 3-aminobenzophenone building blocks is shown in Scheme 7B. The acid chlorides **35b** of substituted 3-nitrobenzoic acids **35a** were prepared using excess oxalyl chloride in dichloromethane. Oxalyl chloride was the reagent of choice due to the low-boiling nature of the reagent, permitting the use of excess and purification by straightforward evaporation of volatiles. The solution was typically stirred at room temperature for 4 h followed by evaporation of the oxalyl chloride and solvent. In the same reaction vials, a Friedel–Crafts acylation reaction was performed by the addition of benzene followed by aluminum trichloride. The solution was stirred at room temperature overnight or for 4 h when alkoxy substituents were present. Upon completion of the reaction, purification was accomplished by an aqueous extraction, followed by addition of magnesium sulfate and the CMR/R polymer **8** to afford the pure substituted 3-nitrobenzophenones **36**. Compounds **36** were reduced in a similar manner as stated above to afford 3-aminobenzophenone **37** building blocks with substituents present on the aniline ring.

The substituted 3-aminobenzophenones **34** and **37** were then reacted with the acid chloride **25** in an array library format (Scheme 8), followed by purification with the CMR/R polymer **8** to afford pure pyrazolecarboxamides **38** substituted at R_2 with electron-donating substituents (R_1 = H; Table 5) and pyrazolecarboxamides **39** substituted at R_1 (R_2 = H; Table 6).[14]

After biological evaluation of the analogs from Tables 4–6, it was determined that compound **27o** had a 4-fold increase in herbicidal activity compared to the initial lead **3**. Thus, lead refinement with the synthesis in Scheme 9 was carried out to prepare other amide analogs of compound **27o**. The pyrazole acid chloride **25** and ethyl 3-aminobenzoate (**40**) were reacted to yield 3-[[[3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]benzoic acid, ethyl ester (**27m**). The ethyl ester **27m** was hydrolyzed to the 3-[[[3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]benzoic acid (**41**) using potassium carbonate in a mixture of methanol and water. The acid **41** was then reacted with P-EDC (**4**) to form the anhydride followed by addition of amine to afford the crude product **42**. The same purification protocol as described for Scheme 3 was utilized to yield the pure products **42**. Compounds prepared by this route are shown in Table 7.

Conclusion

Use of our recently reported chemical library purification strategy based on principles of molecular recognition

(14) The Friedel–Crafts acylation reactions (Scheme 7) afforded regioisomers in several cases and were purified at some point in the synthesis. The two exceptions are compounds **39j,k**, in which each contains a mixture of regioisomers.

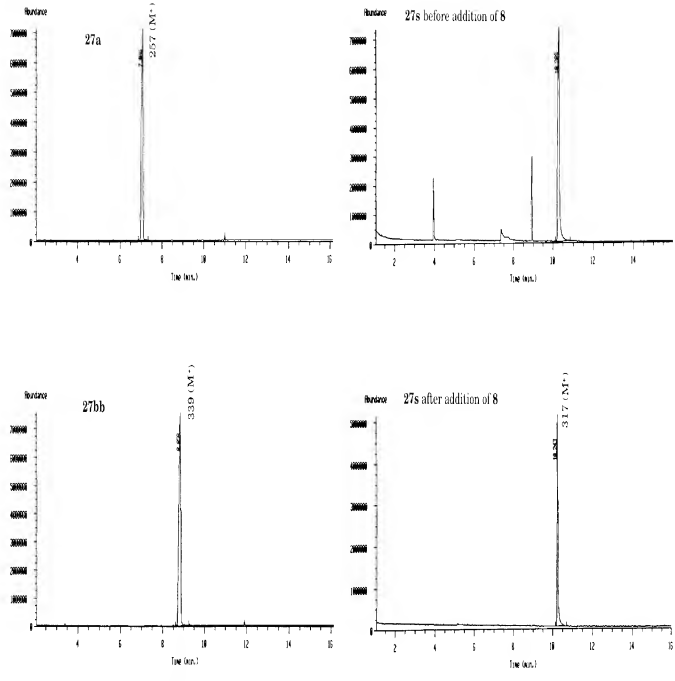
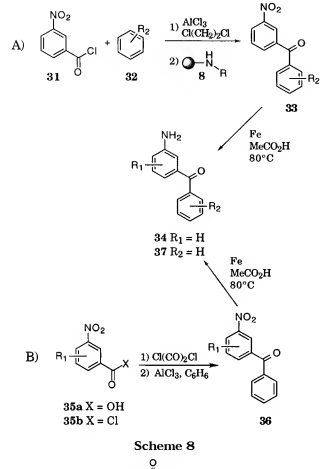
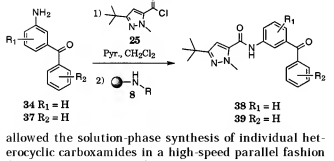


Figure 1. GC/MS electrograms of compounds *27a,s,bb*.

Scheme 7



Scheme 8



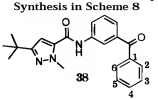
allowed the solution-phase synthesis of individual heterocyclic carboxamides in a high-speed parallel fashion (typically 10–30 mg each). Polymeric reagents were used in the synthesis to generate reactive species involved in product formation, and complementary molecular reactivity/molecular recognition polymer **8** (CMR*R* polymer **8**) was used to remove unreacted or derivatized starting materials from reaction mixtures to afford essentially pure products, irrespective of the reaction yields. This technique was utilized in the preparation of building blocks and primary screening libraries, as well as lead refinement libraries. Although not illustrated herein, the strategy is not limited to the parallel synthesis of individual compounds and is also applicable to compound mixtures. The high-speed parallel synthesis allowed for the preparation and screening of over 400 compounds in a timely manner[15] resulting in compound **27o** with a 4-fold improvement in herbicidal activity over the lead **3**.

Experimental Section

General. Melting points were determined with a capillary melting point apparatus and are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded using 360 and 400 MHz NMR spectrometers. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA. Sample purity was determined by GLC analysis utilizing a capillary column (0.53 mm i.d., DB-1 bonded phase, 1.5 μm film thickness, 30 m). Normally, a temperature program from 100 to 300 °C at 15 °C/min was employed. Column chromatography was performed on a preparative liquid chromatography instrument using silica gel columns. Reported yields are unoptimized with emphasis on purity of products rather than quantity.

General Procedure A. Amide Formation from Carboxylic Acid 5 To Afford Heterocyclic Carboxamides 7 (Tables 1–3 and Scheme 3). The carboxylic acid **5** (0.30 mmol) completely dissolved in dichloromethane (2 mL) (or in a dichloromethane/dimethyl formamide solution) was added

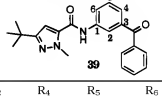
Table 5. Pyrazolecarboxamides 38 Prepared by the Synthesis in Scheme 8



compd	R_2	R_3	R_4	R_5	R_6	% yield[c]
38a	H	H	Me	H	H	80
38b	H	H	F	H	H	79
38c	H	H	OMe	H	H	76
38d	OMe	H	OMe	H	H	72
38e	Cl	H	F	Me	H	69
38f	H	Cl	Cl	H	H	70
38g	F	H	Cl	Me	H	65
38h	F	H	H	OH	H	67
38i	F	H	OH	H	H	69
38j	F	H	OMe	H	H	60
38k[b]	F	H	H	Me	H	61
38l	H	H	cyclohexyl	H	H	93
38m	Me	Me	Me	H	H	87
38n	H	H	pentyl	H	H	84
38o	$CH(Me)_2$	H	$CH(Me)_2$	H	H	94
38p	cyclohexyl	H	cyclohexyl	H	H	86
38q	H	H	CH_2(cyclohexyl)	H	H	92
38r	H	H	OBu	H	H	88
38s	H	OMe	OMe	H	H	82

[a] A 61:39 mixture of regioisomers determined by ^{1}H NMR. [b] A 70:30 mixture of regioisomers determined by ^{1}H NMR. [c] Yields are based on mass recovery.

Table 6. Pyrazolecarboxamides 39 Prepared by the Synthesis in Scheme 8



compd	R_2	R_4	R_5	R_6	% yield[a]
39a	H	Cl	H	H	75
39b	H	H	H	Cl	91
39c	H	H	H	CF_3	35
39d	Me	H	H	H	88
39e	H	H	CF_3	H	100
39f	H	H	H	Me	80
39g	CO_2Me	H	H	H	95
39h	H	H	CO_2Me	H	81
39i	H	H	H	OMe	79
39j	H	H	H	CO_2Me	95
39k	OMe	OMe	H	H	100
39l	H	H	H	$N(CH_2)_5$	86
39m	H	H	H	SO_2Me	84

[a] Yields are based on mass recovery.

(15) It took an equivalent of one person working 7 months for both validation and generation of the 400-membered library.

Scheme 9

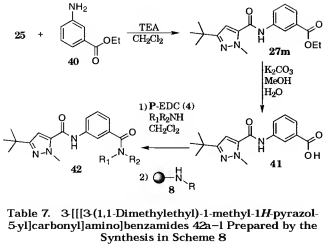
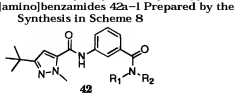


Table 7. 3-[[[3-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]benzamides 42a–l Prepared by the Synthesis in Scheme 8



compd	R_1	R_2	% yield[a]
42a	Pr	H	78
42b	Ph	H	69
42c	Me	H	82
42d	Me	Me	99
42e	Me	Ph	63
42f	Me	CH_2CHCH_2	58
42g	Me	CH_2CCH	77
42h	Et	Et	98
42i	CH_2CHCH_2	CH_2CHCH_2	65
42j	$-(CH_2)_2NMe(CH_2)_2-$		72
42k	$-(CH_2)_2O(CH_2)_2-$		71
42l	$-(CH_2)_5-$		68

[a] Yields were based on mass recovery.

to a suspension of P-EDC[9] (**4**), in dichloromethane (2 mL) at 0 °C. After the mixture stirred at room temperature for 30 min, the aniline **2** (0.10 mmol) was added, and the suspension was heated to 50 °C. The suspension was stirred at 50 °C for 1 h to 7 days.

When the aniline **2** had completely reacted, the CMR*A*R polymer **8** (2.36 mmol/g) (200 mg, 0.472 mmol) was added and stirred for 15 min. The solution was filtered, and the polymer was rinsed with dichloromethane, tetrahydrofuran (BHT free), and dichloromethane until no more UV activity was seen in the dichloromethane washing. The solvent was removed to afford the pure product **7**.

If the aniline **2** had not completely reacted and some product was seen, hexafluoroisopropyl oxalate (**11**) (0.050 g, 0.146 mmol) was added and the solution was stirred at 50 °C for 1–24 h. The CMR*A*R polymer **8** (2.36 mmol/g) (200 mg, 0.472 mmol) was then added and stirred for 15 min. The solution was filtered, and the polymer was rinsed with dichloromethane, tetrahydrofuran (BHT free), and dichloromethane until no more UV activity was seen in the dichloromethane washing. The solvent was removed to afford the pure product **7**. All products were characterized by MS, and some were characterized by ^{1}H NMR as listed below.

7a: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 1.00 (s, 9H), 2.72 (s, 2H), 4.43 (s, 3H), 7.51 (m, 7H), 7.80 (d, 2H), 8.18 (m, 1H), 8.23 (bs, 1H).

7b: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 2.31 (s, 3H), 4.16 (s, 3H), 6.47 (s, 1H), 7.56 (m, 5H), 7.85 (m, 4H), 8.03 (d, 1H).

7c: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 2.34 (s, 3H), 3.90 (s, 3H), 7.51 (m, 5H), 7.85 (m, 2H), 7.92 (s, 1H), 8.20 (d, 1H), 8.80 (bs, 1H).

7d: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 4.23 (s, 3H), 6.71 (d, 1H), 7.57 (m, 6H), 7.82 (m, 2H), 7.89 (s, 1H), 7.95 (s, 1H), 8.05 (dd, 1H).

7e: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 1.42 (s, 9H), 6.20 (s, 2H), 7.50 (m, 10H), 7.81 (d, 2H), 8.12 (d, 1H), 8.21 (d, 1H), 9.17 (bs, 1H).

7f: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 1.72 (s, 9H), 2.29 (s, 3H), 6.38 (s, 1H), 7.54 (m, 5H), 7.83 (m, 4H), 8.08 (d, 1H).

7k: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 1.42 (s, 9H), 4.01 (s, 3H), 6.69 (s, 1H), 7.53 (m, 5H), 7.84 (m, 2H), 7.87 (d, 1H), 7.95 (s, 1H), 8.12 (dd, 1H), 8.78 (bs, 1H).

7o: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 3.94 (s, 3H), 4.27 (s, 3H), 7.50 (m, 5H), 7.84 (d, 2H), 7.97 (d, 1H), 8.14 (dd, 1H), 8.80 (bs, 1H).

7p: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 1.58 (s, 9H), 4.09 (s, 3H), 7.25 (s, 1H), 7.52 (m, 5H), 7.84 (m, 2H), 7.95 (s, 1H), 8.14 (d, 1H), 8.74 (bs, 1H).

7q: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 4.13 (s, 3H), 7.52 (m, 5H), 7.84 (d, 2H), 7.91 (s, 1H), 8.20 (d, 1H), 8.74 (bs, 1H).

7A: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 7.13 (m, 1H), 7.53 (m, 5H), 7.69 (m, 1H), 7.82 (m, 2H), 7.97 (m, 2H), 8.08 (d, 1H).

7C: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 6.95 (d, 1H), 7.53 (m, 6H), 7.81 (d, 2H), 7.90 (s, 1H), 7.99 (s, 1H), 8.05 (s, 1H), 8.08 (d, 1H).

7M: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 2.72 (s, 3H), 2.74 (s, 3H), 7.50 (m, 6H), 7.83 (m, 3H), 8.03 (d, 1H).

7P: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 1.35 (d, 3H), 1.37 (d, 3H), 3.70 (sept, 1H), 7.54 (m, 6H), 7.84 (m, 3H), 8.02 (d, 1H).

7W: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 7.39 (m, 3H), 7.57 (m, 7H), 7.77 (m, 2H), 7.79 (m, 2H).

7X: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 1.51 (s, 9H), 7.52 (m, 4H), 7.63 (m, 2H), 7.82 (m, 3H), 7.98 (m, 2H).

7Z: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 7.53 (m, 6H), 7.85 (m, 6H), 8.05 (m, 2H), 9.19 (bs, 1H).

7aa: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 7.13 (d, 1H), 7.38 (t, 1H), 7.66 (m, 11H), 8.22 (bs, 1H).

7bb: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 7.52 (m, 6H), 7.83 (m, 3H), 7.95 (s, 1H), 8.17 (m, 1H).

7ii: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 7.55 (m, 5H), 7.85 (dd, 2H), 8.05 (s, 1H), 8.20 (dd, 1H), 8.62 (s, 1H), 8.85 (s, 1H), 9.54 (d, 1H), 9.82 (bs, 1H).

7jj: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 2.76 (s, 3H), 7.55 (m, 5H), 7.66 (dd, 2H), 8.05 (s, 1H), 8.19 (d, 1H), 8.52 (s, 1H), 9.40 (s, 1H), 9.76 (bs, 1H).

7ll: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 7.56 (m, 5H), 7.76 (s, 2H), 7.79 (m, 2H), 7.81 (m, 1H), 8.02 (m, 1H), 8.70 (s, 1H).

Preparation of the CMR*A*R Polyamine Polymer 8. Merrifield's resin (**14**) (2% cross-linked, 1.07 mmol/g) (10.67 g, 0.114 mol) was added to diethylenetriamine (**15**) (0.382 g, 2.19 mol) and the mixture heated at 100 °C for 4 h. The polymer was filtered and successively rinsed two times with 10% triethylamine in dimethylformamide, once with dimethylformamide, four times with 10% triethylamine in tetrahydrofuran, three times with tetrahydrofuran, and three times with methanol. The CMR*A*R polymer **8** was then dried under vacuum to a constant weight. Anal. Obsd: Cl, 0.0; N, 3.31; this corresponds to 2.36 mmol/g, 64% monoalkylation, and 36% dialkylation.

Bis(hexafluoroisopropyl) Oxalate (11). The following reaction utilized oven-dried glassware, and the reaction mixture and product were maintained under a dry nitrogen atmosphere at all times. Hexafluoro-2-propanol (9.0 mL, 85.5 mmol) was dissolved in anhydrous ether (20 mL), the mixture was cooled in an ice bath, and oxalyl chloride (3.50 mL, 40.1 mmol) was added. An anhydrous ether solution (10.0 mL) of triethylamine (10.95 mL, 80.3 mmol) was then added dropwise with stirring over a 45 min period. White solids formed immediately, and the mixture was stirred overnight allowing the ice in the ice bath to melt. The mixture was carefully filtered, rinsing with a minimum of anhydrous ether. The filtrate was then distilled at atmospheric pressure to remove

the bulk of the ether. When the distillate temperature reached 43 °C, the pot remains were transferred to a smaller flask and the distillation was continued. The product fraction was collected at 126–127 °C to afford 10.33 g (66%) of a clear oil of **11**: ^{1}H NMR (CDCl$_3$) ppm 5.81 (heptet, J = 5.5 Hz, 1H); ^{13}C NMR (CDCl$_3$) ppm 152.2 (s), 119.6 (q, J = 282.9 Hz), 68.9 (heptet, J = 35.8 Hz); ^{19}F NMR (CDCl$_3$) −74.144 (doublet, J = 5.4 Hz).

5,5-Dimethyl-2,4-dioxohexanoic Acid, Ethyl Ester (20).[16] Sodium metal (7.4 g, 3.21 mol) was added in small portions to ethanol (1.5 L) and stirred until all of the sodium had reacted. Ethyl oxalate (**19**) (233.0 g, 1.6 mol) was added, followed by dropwise addition of pinacolone (**18**) (160.2 g, 1.6 mol). The solution was stirred at room temperature for 5 h and then poured over ice/hydrochloric acid, followed by extraction with ether. The organic layer was then washed with 4 N hydrochloric acid, water, and brine. The solution was dried over magnesium sulfate and filtered, and the solvent was removed to give the crude product. The product was purified by column chromatography (5% ethyl acetate−hexane) to give 344 g (93%) of an orange oil of **20**. ^{1}H NMR (CDCl$_3$) ppm 1.25 (s, 9H), 1.40 (t, 3H), 4.37 (q, 3H), 6.56 (s, 1H).

3-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazole-5-carboxylic Acid, Ethyl Ester (21). Methyl hydrazine (23.0 g, 0.50 mol) was added dropwise to a solution of compound **20** (100.0 g, 0.50 mol) in acetic acid (1.5 L). The resulting solution was stirred at room temperature for 18 h. The solution was then diluted with ether and brine, the organic layer was washed with brine, dried over magnesium sulfate, and filtered, and the solvent was removed to give the crude product. Fraction 1 of column chromatography (5% ethyl acetate−hexane) gave 72.4 g (68%) of a clear oil of **21**. ^{1}H NMR (CDCl$_3$) ppm 1.35 (s, 9H), 1.42 (t, 3H), 4.17 (s, 3H), 4.37 (q, 2H), 6.72 (s, 1H); ^{13}C NMR (CDCl$_3$) ppm 13.4, 29.6, 31.1, 38.3, 59.9, 106.4, 131.7, 159.2, 159.5. Anal. Calcd for $C_{11}H_{18}O_2N_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.75; H, 8.69; N, 13.22.

5-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazole-3-carboxylic Acid, Ethyl Ester (22). Following the same procedure described for **21**, fraction 2 of column chromatography (5% ethyl acetate−hexane) gave 12.1 g (12%) of a yellow oil of **22**. ^{1}H NMR (CDCl$_3$) ppm 1.39 (t, 3H), 1.40 (s, 9H), 4.05 (s, 3H), 4.39 (q, 2H), 6.60 (s, 1H); ^{13}C NMR (CDCl$_3$) ppm 13.5, 28.5, 30.3, 39.3, 59.8, 105.7, 140.5, 151.9, 161.6. Anal. Calcd for $C_{11}H_{18}O_2N_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.56; H, 8.68; N, 13.11.

3-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazole-5-carboxylic Acid (23). Aqueous sodium hydroxide (10%) (19 mL, 0.47 mol) was added to a solution of compound **21** (67.0 g, 0.319 mol) in ethanol (1.2 L), and the resulting solution stirred at room temperature for 18 h. The solution was then poured over ice/hydrochloric acid and extracted with ether. The organic layer was washed with brine, dried over magnesium sulfate, and filtered, and the solvent was removed to give 53.9 g (93%) of a white solid of **23**: mp 155–156 °C; ^{1}H NMR (CDCl$_3$) ppm 1.38 (s, 9H), 4.22 (s, 3H), 6.86 (s, 1H); ^{13}C NMR (CDCl$_3$) ppm 29.5, 31.0, 38.2, 107.8, 131.1, 159.8, 163.0. Anal. Calcd for $C_9H_{14}O_2N_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.55; H, 7.78; N, 15.43.

5-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazole-3-carboxylic Acid (24). Following the same procedure described for compound **23**, compound **22** (12.0 g, 0.057 mol) and aqueous sodium hydroxide (10%) (23.0 mL, 0.073 mol) were used to give 7.29 g (70%) of a white solid of **24**: mp 168–169 °C; ^{1}H NMR (CDCl$_3$) ppm 1.45 (s, 9H), 4.12 (s, 3H), 6.71 (s, 1H); ^{13}C NMR (CDCl$_3$) ppm 28.2, 31.1, 39.1, 105.8, 138.6, 152.3, 166.0. Anal. Calcd for $C_9H_{14}O_2N_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.40; H, 7.76; N, 15.35.

3-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazole-5-carbonyl Chloride (25). To a solution of compound **23** (25.0 g, 137.2 mmol) in dichloromethane was added oxalyl chloride (87.0 g, 685.4 mmol) followed by 1 drop of dimethyl formamide. After stirring at room temperature for 16 h the solvent was removed to give 26.58 g (97%) of a clear oil of **25**: ^{1}H NMR (CDCl$_3$) ppm 1.37 (s, 9H), 4.13 (s, 3H), 6.99 (s, 1H); ^{13}C NMR (CDCl$_3$) ppm 30.2, 32.0, 39.8, 113.2, 135.0, 157.9, 160.8.

General Procedure B. Reaction of 3-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazole-5-carbonyl Chloride (25) with Anilines To Afford the Pyrazolecarboxamides 27, 38, and 39 (Tables 4−6 and Schemes 6, 8). Under conditions of parallel reaction synthesis, pyridine (0.12 mmol) was added to a solution of **25** (0.12 mmol) and aniline (0.10 mmol) in dichloromethane, and the resulting solution was stirred at room temperature for 2–24 h. The CMR/R polymer **8** (2.95 mmol/g) (3.00 mg, 0.472 mmol) was added and stirred for 15 min. The solution was filtered, and the polymer was rinsed with dichloromethane, tetrahydrofuran (BHT free), and dichloromethane until no more UV activity was seen in the dichloromethane washing. The solvents were removed to afford the pure product. Yields were in the range of 35–100%. All products were characterized by MS, and a portion were further characterized as listed below.

27c: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.36 (s, 9H), 2.59 (s, 3H), 4.18 (s, 3H), 6.56 (s, 1H), 7.70 (d, 1H), 7.86 (dd, 1H), 7.96 (bs, 1H), 8.20 (d, 1H).

27e: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.45 (s, 9H), 2.67 (s, 3H), 4.37 (s, 3H), 6.62 (s, 1H), 7.56 (d, 1H), 7.76 (dd, 1H), 8.19 (bs, 1H), 9.01 (m, 1H).

27g: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.36 (s, 9H), 2.75 (m, 2H), 3.15 (m, 2H), 4.18 (s, 3H), 6.65 (s, 1H), 7.53 (dd, 1H), 7.80 (d, 1H), 8.11 (bs, 1H), 9.11 (m, 1H).

27h: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.35 (s, 9H), 1.87 (m, 4H), 2.77 (m, 2H), 2.95 (m, 2H), 4.17 (s, 3H), 6.51 (s, 1H), 7.27 (m, 1H), 7.65 (d, 1H), 7.80 (bs, 1H), 8.00 (dd, 1H).

27m: general procedure B yielded a white solid, mp 114–115 °C; ^{1}H NMR (CDCl$_3$) ppm 1.45 (s, 9H), 4.12 (s, 3H), 6.71 (s, 1H). Anal. Calcd for $C_{19}H_{14}O_2N_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.40; H, 7.76; N, 15.35.

27o: general procedure B yielded a white solid, mp 141–142 °C; ^{1}H NMR (CDCl$_3$) ppm 1.16 (bt, 3H), 1.29 (bt, 3H), 1.39 (s, 9H), 3.31 (bq, 2H), 3.59 (bq, 2H), 4.18 (s, 3H), 6.76 (s, 1H), 7.05 (bd, 1H), 7.37 (t, 1H), 7.39 (bs, 1H), 7.74 (bd, 1H), 8.81 (bs, 1H). Anal. Calcd for $C_{20}H_{28}O_2N_4$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.48; H, 7.93; N, 15.67.

27q: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.26 (t, 3H), 1.30 (s, 9H), 4.02 (s, 2H), 4.17 (s, 3H), 4.25 (q, 2H), 6.56 (s, 1H), 7.50 (m, 2H), 7.74 (d, 1H), 7.98 (m, 2H), 8.08 (s, 1H).

27t: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.35 (s, 9H), 3.85 (s, 3H), 4.17 (s, 3H), 6.48 (s, 1H), 6.73 (dd, 1H), 7.05 (d, 1H), 7.28 (m, 2H), 7.62 (bs, 1H).

27u: general procedure B yielded a white solid, mp 94–95 °C; ^{1}H NMR (CDCl$_3$) ppm 1.36 (s, 9H), 4.20 (s, 3H), 4.59 (sept, 1H), 6.51 (s, 1H), 6.72 (dd, 1H), 7.04 (d, 1H), 7.25 (m, 1H), 7.33 (s, 1H), 7.70 (bs, 1H). Anal. Calcd for $C_{19}H_{25}O_2N_3$: C, 68.54; H, 7.99; N, 27.32. Found: C, 68.23; H, 7.93; N, 13.15.

27v: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.35 (s, 9H), 4.18 (s, 3H), 6.53 (s, 1H), 7.45 (m, 1H), 7.51 (m, 1H), 7.82 (m, 2H), 7.91 (bs, 1H).

27w: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.36 (s, 9H), 4.19 (s, 3H), 6.57 (s, 1H), 7.57 (t, 1H), 7.91 (bs, 1H), 8.05 (dd, 2H), 8.49 (m, 1H).

27cc: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.35 (s, 9H), 4.17 (s, 3H), 6.51 (s, 1H), 6.94 (m, 2H), 7.72 (bs, 1H), 8.28 (m, 1H).

27dd: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.36 (s, 9H), 4.19 (s, 3H), 7.42 (m, 5H), 7.58 (m, 3H), 7.74 (bs, 1H), 7.84 (s, 1H).

27ee: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.35 (s, 9H), 4.16 (s, 3H), 6.54 (s, 1H), 7.56 (m, 4H), 7.73 (dd, 1H), 7.83 (bs, 1H), 7.99 (m, 4H).

27ff: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.34 (s, 9H), 4.15 (s, 3H), 6.47 (s, 1H), 6.82 (m, 1H), 7.17 (m, 3H), 7.30 (m, 5H), 7.64 (bs, 1H).

27ii: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.37 (s, 9H), 4.22 (s, 3H), 6.76 (s, 1H), 7.15 (t, 1H), 7.50 (m, 2H), 7.63 (m, 3H), 7.75 (m, 2H), 8.76 (dd, 1H).

27jj: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.36 (s, 9H), 4.19 (s, 3H), 6.55 (s, 1H), 7.54 (t, 2H), 7.82 (m, 6H).

(16) Seki, S.; Yamaguchi, H.; Nakamura, Y.; Kubo, H. Japanese Patent SHO 57-100666, 1982.

38b: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.46 (s, 9H), 4.46 (s, 3H), 7.21 (m, 3H), 7.54 (m, 2H), 7.87 (m, 2H), 8.10 (m, 2H), 9.68 (bs, 1H).

38e: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.51 (s, 9H), 2.31 (s, 3H), 4.57 (s, 3H), 7.16 (d, 1H), 7.25 (s, 1H), 7.29 (m, 1H), 7.41 (m, 1H), 7.49 (m, 1H), 8.21 (m, 1H), 8.27 (bs, 1H).

38f: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.46 (s, 9H), 4.49 (s, 3H), 7.31 (s, 1H), 7.52 (m, 4H), 7.90 (s, 1H), 8.20 (d, 1H), 8.25 (s, 1H), 10.01 (bs, 1H).

38g: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.33 (s, 9H), 2.41 (s, 3H), 4.17 (s, 3H), 6.63 (s, 1H), 7.22 (d, 1H), 7.48 (m, 3H), 7.80 (bs, 1H), 7.89 (s, 1H), 8.07 (dd, 1H).

38i: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.49 (s, 9H), 4.52 (s, 3H), 6.63 (m, 1H), 6.75 (dd, 1H), 7.49 (m, 3H), 7.69 (m, 1H), 8.18 (m, 1H), 8.19 (m, 1H).

38n: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 0.91 (t, 3H), 1.32 (m, 4H), 1.45 (s, 9H), 1.65 (m, 2H), 2.68 (t, 2H), 4.49 (s, 3H), 7.28 (m, 2H), 7.49 (m, 3H), 7.72 (m, 2H), 8.17 (m, 2H).

38o: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.20 (m, 12H), 1.49 (s, 9H), 2.92 (m, 2H), 4.55 (s, 3H), 7.05 (s, 1H), 7.36 (m, 6H), 8.11 (m, 1H), 8.33 (bs, 1H).

38q: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.18 (m, 7H), 1.47 (s, 9H), 1.70 (m, 2H), 2.57 (d, 2H), 4.51 (s, 3H), 7.27 (m, 2H), 7.54 (m, 4H), 7.73 (m, 2H), 8.19 (m, 2H).

38a: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.44 (s, 9H), 4.48 (s, 3H), 6.83 (s, 1H), 7.43 (m, 4H), 7.60 (m, 1H), 7.79 (m, 2H), 8.00 (s, 1H), 8.12 (dd, 1H).

39b: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.32 (s, 9H), 4.16 (s, 3H), 6.54 (s, 1H), 7.55 (m, 5H), 7.85 (dd, 1H), 8.23 (bs, 1H), 8.85 (s, 1H).

39d: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.50 (s, 9H), 2.25 (s, 3H), 4.45 (s, 3H), 7.28 (m, 3H), 7.48 (m, 2H), 7.67 (m, 2H), 7.82 (d, 2H), 9.63 (bs, 1H).

39e: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.47 (s, 9H), 4.51 (s, 3H), 7.28 (m, 2H), 7.53 (m, 3H), 7.81 (m, 3H), 8.60 (s, 2H).

39f: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.35 (s, 9H), 2.43 (s, 3H), 4.16 (s, 3H), 6.52 (s, 1H), 7.39 (d, 1H), 7.53 (m, 2H), 7.62 (m, 3H), 7.84 (d, 2H), 8.17 (d, 1H).

39g: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.40 (s, 9H), 3.51 (s, 3H), 4.30 (s, 3H), 6.70 (s, 1H), 7.18 (dd, 1H), 7.60 (m, 6H), 7.79 (m, 1H), 8.85 (d, 1H).

39h: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.34 (s, 9H), 3.96 (s, 3H), 4.17 (s, 3H), 6.61 (s, 1H), 7.53 (m, 2H), 7.65 (m, 1H), 7.85 (d, 2H), 8.19 (d, 2H), 8.23 (d, 1H), 8.56 (s, 1H).

39i: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.44 (s, 9H), 4.05 (s, 3H), 4.33 (s, 3H), 6.57 (s, 1H), 7.05 (d, 1H), 7.58 (m, 4H), 7.83 (dd, 2H), 8.37 (bs, 1H), 8.84 (s, 1H).

39j: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.38 (s, 9H), 4.04 (s, 3H), 4.17 (s, 3H), 6.73 (s, 1H), 7.52 (m, 5H), 7.87 (d, 2H), 8.20 (d, 1H), 9.15 (s, 1H).

39k: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.33 (s, 9H), 3.73 (s, 3H), 3.74 (s, 3H), 4.19 (s, 3H), 6.43 (s, 1H), 6.80 (m, 2H), 7.48 (m, 2H), 7.61 (m, 1H), 7.87 (m, 2H), 8.08 (bs, 1H), 8.38 (d, 1H).

39m: general procedure B; ^{1}H NMR (CDCl$_3$) ppm 1.50 (s, 9H), 3.22 (s, 3H), 4.50 (s, 3H), 6.75 (s, 1H), 7.57 (m, 2H), 7.74 (m, 2H), 7.89 (m, 2H), 8.13 (d, 1H), 8.97 (s, 1H).

Compounds 27y,aa. Compound **25** (0.12 mmol) was added dropwise to a solution of the aniline (0.010 mmol) in pyridine (5 mL). The solution was stirred at 80 °C overnight. The mixture was poured into ice water and extracted with ether, and the resultant organic layer was washed with 2 N hydrochloric acid, water, and brine. The solution was dried over magnesium sulfate and filtered, and the solvent was removed to give the crude product. The product was purified by preparative thin layer chromatography. Compound **27y**: EI-MS *m/e* 370 (M^+), 355 ($M^+ - Me$), 165 (pyrazoleCO$^+$). Compound **27aa**: EI-MS *m/e* 369 (M^+), 354 ($M^+ - Me$), 165 (pyrazoleCO$^+$).

General Procedure C. Friedel–Crafts Acylation with 3-Nitrobenzoyl Chloride (31) To Afford the Substituted 3-Nitrobenzophenone 33 (Scheme 7). Under conditions of parallel reaction synthesis, aluminum trichloride (0.17 g, 1.3 mmol) was added to a solution of 3-nitrobenzoyl chloride (**31**) (0.16 g, 1.10 mmol) and substituted benzene derivative **32** (1.0 mmol) in 1,2-dichloroethane (4 mL). The solution was stirred at room temperature for 4 h when alkoxy substituents were used and overnight for all other aromatic compounds. The mixture was poured into water and extracted with dichloromethane. The resultant organic layer was washed with water and brine. The solution was dried over magnesium sulfate followed by addition of the CMR/R polymer **8** (2.36 mmol/g) (200 mg, 0.472 mmol) and then stirred for 15 min. The solution was filtered, and the polymer was rinsed with dichloromethane, tetrahydrofuran (BHT free), and dichloromethane until no more UV activity was seen in the eluant. The solvent was removed to afford the substituted nitrobenzophenone **33**. The purity of products was determined by GC, and some products were characterized by MS.

General Procedure D. Reduction of the 3-Nitrobenzophenones 33 and 36 with Iron To Afford the 3-Aminobenzophenones 34 and 37 (Scheme 7). The substituted nitrobenzophenone **33** or **36** (1.0 mmol) was stirred in glacial acetic acid (4 mL). The solution was heated to 80 °C, and powdered iron (0.28 g, 5.0 mmol) was added with vigorous stirring. The solution was stirred at 80 °C for 15–60 min at which point the iron had turned gray. The reaction mixture was filtered through Celite, and the solid was washed with dichloromethane. The resultant organic layer was washed with water, stirred with saturated sodium bicarbonate, and washed with water again. The solution was dried over magnesium sulfate and filtered, and the solvent was removed to afford the substituted aminobenzophenone product **34** or **37**. When necessary, the product was purified by preparative thin layer chromatography. All products were characterized by MS, and a portion were characterized by ^{1}H NMR.

General Procedure E. Acid Chloride Formation from the Substituted 3-Nitrobenzoic Acid 35a (Scheme 7). To a solution of substituted 3-nitrobenzoic acid **35a** (1.0 mmol) in dichloromethane was added oxalyl chloride (0.64 g, 5.0 mmol) followed by 1 drop of dimethylformamide. After stirring at room temperature for 1–24 h, the solvent was removed to afford the substituted 3-nitrobenzoyl chloride **35b**. The crude products were carried on to the next step without characterization.

General Procedure F. Friedel–Crafts Acylation with Substituted 3-Nitrobenzoyl Chloride 35b and Benzene To Afford the Substituted 3-Nitrobenzophenone 36 (Scheme 7). To a solution of the substituted 3-nitrobenzoyl chloride **35b** (1.0 mmol) in benzene was added aluminum trichloride (0.17 g, 1.3 mmol). The solution was stirred at room temperature for 4 h for alkoxy substituents and overnight for other aromatic compounds. The mixture was poured into water and extracted with dichloromethane, and the resultant organic layer was washed with water and brine. The solution was dried over magnesium sulfate followed by addition of the polymer **8** (2.36 mmol/g) (423 mg, 1.0 mmol) and stirred for 15 min. The solution was filtered, and the polymer was rinsed with dichloromethane, tetrahydrofuran (BHT free), and dichloromethane until no more UV activity was seen in the eluant. The solvent was removed to afford the substituted nitrobenzophenone **36**. The purity of products was determined by GC, and some products were characterized by MS.

3-[[3-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl-carbonyl]amino]benzoic Acid, Ethyl Ester (27aa). Compound **25** (2.0 g, 1.0 mmol) was added to a solution of ethyl 3-aminobenzoate (**40**) (1.65 g, 1.0 mmol) and triethylamine (0.11 g, 1.0 mmol) in dichloromethane (30 mL). After stirring at room temperature for 16 h, the mixture was washed with water and brine, dried over magnesium sulfate, and filtered, and the solvent was removed to give the crude product **27m**. The product was purified by column chromatography (20% ethyl acetate–hexane) to give 2.02 g (61%) of a white solid of **27m**: mp 114–115 °C; ^{1}H NMR (CDCl$_3$) ppm 1.37 (s, 9H), 1.44 (t, 3H), 4.20 (s, 3H), 4.43 (q, 2H), 6.59 (s, 1H), 7.49 (t, 1H), 7.88 (m, 1H), 7.95 (bs, 1H), 8.07 (m, 2H). Anal. Calcd for $C_{19}H_{23}O_3N_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.63; H, 7.05; N, 12.68.

3-[[[3-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl-]carbonyl]amino]benzoic Acid (41). Potassium carbonate (6.0 g, 43.4 mmol) was added to a solution of compound **27m** (1.82 g, 5.5 mmol) in a 2:1 mixture of methanol/water. The solution was stirred at room temperature for 18 h. The solution was poured over ice/hydrochloric acid and extracted with ether. The organic layer was washed with brine, dried over magnesium sulfate, and filtered, and the solvent was removed to give 1.5 g (91%) of a white solid of **41**: mp 245 °C dec; ^{1}H NMR (CDCl$_3$) ppm 1.27 (s, 9H), 4.02 (s, 3H), 6.98 (s, 1H), 7.46 (t, 1H), 7.67 (d, 1H), 7.98 (bd, 1H), 8.36 (s, 1H), 10.21 (s, 1H), 12.95 (bs, 1H).

3-[[[3-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl-]carbonyl]amino]benzamides 42 (Table 7). These compounds were prepared according to the general procedure given above for Scheme 3 using 3-[[[3-(1,1-dimethylethyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl]amino]benzoic acid (**41**). All products were characterized by MS, and a portion were characterized by ^{1}H NMR as listed below.

3-(1,1-Dimethylethyl)-1-methyl-*N*-[3-[(methyl-2-propynylamino)carbonyl]phenyl]-1*H*-pyrazole-4-carboxamide (42g): ^{1}H NMR (CDCl$_3$) ppm 1.38 (s, 9H), 1.67 (bs, 2H), 2.37 (bs, 1H), 3.10 (bs, 3H), 4.18 (s, 3H), 6.56 (s, 1H), 7.18 (bm, 1H), 7.37 (t, 1H), 7.57 (bs, 1H), 7.76 (bm, 1H), 8.29 (bs, 1H).

3-(1,1-Dimethylethyl)-1-methyl-*N*-[3-(morpholinocarbonyl)phenyl]-1*H*-pyrazole-4-carboxamide (42l): ^{1}H NMR (CDCl$_3$) ppm 1.39 (s, 9H), 1.59 (m, 6H), 3.40 (bt, 2H), 3.75 (bt, 2H), 4.19 (s, 3H), 6.70 (s, 1H), 7.10 (bm, 1H), 7.37 (t, 1H), 7.49 (bs, 1H), 7.78 (m, 1H), 8.29 (bs, 1H).

Supporting Information Available: GC/MS data available in tables for compounds **7**, **27**, **38**, **39**, and **42**; ^{1}H NMR available for a random 60% of these compounds; GC/MS data available in tables for building blocks **33**, **34**, **36**, and **37** (70 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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